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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,292	11/28/2001	Muthiah Manoharan	ISIS-4804	3997

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WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE, 46TH FLOOR
1650 MARKET STREET
PHILADELPHIA, PA 19103

EXAMINER

EPFS FORD, JANET L

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 01/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/996,292

Applicant(s)

MANOHARAN ET AL.

Examiner

Janet L. Epps-Ford, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) 6-15, 26-35 and 40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 16-25 and 36-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-332) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3-01-02 6) ☐ Other: _____

Election/Restrictions

1. Applicant's election of the species designated as ISIS # 120745, and corresponding to claims 1-7, 16-26, and 36-40, for prosecution on the merits in the Paper filed 10-15-03 is acknowledged.

2. Claims 8-15, and 27-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Paper filed 10-15-03. Moreover, claims 6-7, 26 and 40 are also withdrawn from consideration since they do not read on the elected invention. Therefore, claims 1-5, 16-25 and 36-39 are currently under examination.

3. Applicant's election with traverse of compounds according to formula V in the Paper filed 10-15-03 is acknowledged. The traversal is on the ground(s) that a reasonable search would necessarily reveal any and all prior disclosures of claimed species, assuming that any exists. This is not found persuasive because Applicant's claims are so broad that the number of species of compounds encompassed by the instant claims is exponential, and the number of categories of distinct classes of compounds encompassed by the claims is also exponential. Additionally, a search of the elected species according to ISIS #120745 comprising 5' and 3' L-thymidine nucleotides would not provide an adequate search of compounds that are structurally distinct from this species of compound, for example compounds comprising 5' and 3' nucleotides comprising 2'-methoxyethoxy modifications.

The requirement is still deemed proper and is therefore made FINAL.

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Claim Rejections - 35 USC § 103

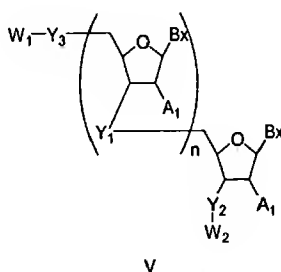
4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1-5, 16-25, and 36-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matulic-Adamic et al. (US Patent No. 5,998,203).

6. It is noted that the particular species ISIS # 120745 was not identified in the prior art, however since the instant claims are not limited to this particular species, a more general search of compounds comprising 5' and/or 3' L-nucleoside modifications was performed by the examiner. This search addresses wherein at least one of W1 and W2 is not a hydrogen or a hydroxyl protecting group, but is a modified nucleoside, in particular an L-nucleoside or L-nucleotide. Moreover, this search addresses wherein at least one internucleoside linking group is not a phosphodiester-linking group. This search is still considered to read on the elected claims, 1-7, 16-26, and 36-39.

7. The instant claims are broadly drawn to compositions according to the following formula V, wherein:



The invention of Matulic-Adamic et al. relates to the incorporation of chemical modifications at the 5' and/or 3' ends of nucleic acids. These terminal modifications are termed as either a 5'-cap or a 3'-cap depending on the terminus that is modified. Certain of these modifications protect the enzymatic nucleic acids from exonuclease degradation. Resistance to exonuclease degradation can increase the half-life of these nucleic acids inside a cell and improve the overall effectiveness of the enzymatic nucleic acids. These terminal modifications can also be used to facilitate efficient uptake of nucleic acids by cells, transport and localization of nucleic acids within a cell, and help achieve an overall improvement in the efficacy of nucleic acids in vitro and in vivo (see col. 2, lines 44-58). The term "chemical modification" as used herein refers to any base, sugar and/or phosphate modification that will protect the enzymatic nucleic acids from degradation by nucleases. One example of these modifications includes, *inter alia*, L-nucleosides (see Figure 7B). Additionally, the invention of Matulic Adamic et al. encompasses wherein the internucleoside linkages have been modified to incorporate phosphorothioate linkages into the 5' end of a nucleic acid structure (see col. 10, lines 9-10).

It would have been obvious at the time the instant invention was made to synthesize oligomeric compounds comprising a structure according to formula V of the instant application, wherein W1 and W2 is not a hydrogen or a hydroxyl protecting group, but is a modified nucleoside, in particular an L-nucleoside or L-nucleotide, moreover, wherein at least one internucleoside linking group is not a phosphodiester-linking group. One of ordinary skill in the art would have been motivated to modify the teachings of Matulic-Adamic et al. to design compound according to the present invention since this reference clearly suggests that designing

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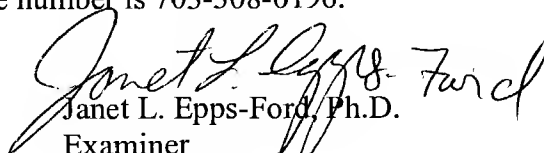
nucleic acid molecules comprising 5' and/or 3' modifications would enhance the biological properties of nucleic acid molecules in comparison their unmodified counterparts.

Therefore, the invention as a whole would have been *prima facie* obvious over Matulic-Adamic et al. at the time invention was made.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE